REMARKS

I. Amendments

The claims are amended to delete reference to hemangioblasts. Claim 2 is clarified; the amendment finds basis at least at page 32 lines 1 to 23. Claims 14 and 15 are amended to reverse the amendments made in the response filed on June 9, 2005. Claims 6, 14 and 15 are amended to depend on claim 1.

Claim 12 is canceled without prejudice or disclaimer. Claims 18 and 19 are added. Claim 18 finds basis at least at page 29 lines 29-35 and page 37 lines 21-31. Claim 19 is the same as claim 6, except that claim 19 refers to the cells defined in claim 18.

Claim 18 is dependent on claim 1 and should be examined with the claims of Group I (claims 1-5).

II. Election / Restrictions

The Examiner has made Restriction final. Applicant continues to traverse.

Group Restriction

The Examiner refuses to rejoin claim 17 with Group I, stating that although claim 17 comprises the matter of claim 3, there are additional features that impose "issues of anticipation and obviousness not present in any of claims 1-5". Applicant disagrees. If the cells of claim 3 are novel and unobvious, then the cells of claim 3 which have the additional feature of being modified, are necessarily also novel and unobvious. This makes the kit of claim 17 also novel and unobvious.

The Examiner states that the previously-submitted amendments to claims 14 and 15 are confusing. These amendments have been reversed. Applicant requests that these claims be rejoined when the product claims are allowable.

The Examiner rejects Applicant's argument that the subject matter of all the claims is sufficiently related that a search of the Group I claims would necessarily encompass Groups

II-VII. The Examiner gives two reasons: that Applicant incorrectly applies a lack-of-unity standard, and that the burden of search includes issues other than searching classes and subclasses. Applicant disagrees.

Section 803 of the MPEP gives guidelines for when restriction is proper:

> "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02."

The Examiner has not met this *prima facie* standard.

Section 808.02 of the MPEP further states:

> "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c) - § 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following:
>
> (A) Separate classification thereof: [....]
>
> (B) A separate status in the art when they are classifiable together: [....]
>
> (C) A different field of search: [....]
>
> Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons exist for dividing among related inventions."

Applicant submits the Examiner has not met this standard for all of the Restriction Groups.

Species Restriction

The Examiner rejects Applicant's argument that searching all the species would not be burdensome. The Examiner refers to there being "six claimed cell types" as contributing to the Examiner's burden. Applicant disagrees.

Applicant does not claim six cell types. With regard to products, Applicant claims a preparation of mammalian cells of which two types are specifically claimed: human and mouse. With regard to methods of making, Applicant claims a method which recites four

cell sources. These sources are clearly related because they are all known to contain stem cells. Section 808.01(a) of the MPEP states:

> "[....] where there is a relationship disclosed between species, such disclosed relation must be discussed and reasons advanced leading to the conclusion that the disclosed relation does not prevent restriction, in order to establish the propriety of restriction."

Applicant submits that the Examiner has not met the standard for establishing proper restriction of species.

Rejoinder

Claims 6 and 19 are directed to methods of making the products of claims 1 and 18 respectively. As permitted by the USPTO's rejoinder practice, claims 6 and 19 should be rejoined when claims 1 and 18 are allowable.

Claims 7 to 11 depend ultimately on claim 6 and should also be rejoined when claim 1 is allowable.

Claims 13 and 16 are directed to methods of using the product of claim 3 and contain all the limitations of claim 3. Claims 14 and 15 are directed to methods of using the product of claim 1 and contain all the limitations of claim 1. Claims 13 to 16 should be rejoined when claims 1 and 3 are allowable.

III. Drawings

The Examiner objects to the drawings as being too dark. A fresh set of drawings is submitted in which all features are clearly visible.

IV. Double Patenting

The Examiner provisionally rejects claims 1 to 4 under 35 U.S.C. 101 as being in conflict with claims of co-pending U.S. application 10/521,071. Applicant has noted the provisional rejection and will ensure that there is no unjustified extension of patent exclusivity beyond the term of patent(s) that may issue.

V. Rejection of claims 1-4 under 35 U.S.C. §112 1st paragraph

The Examiner alleges that claims 1 to 4 do not meet the enablement and written description requirements. Applicant traverses.

Hemangioblasts

The Examiner questions the existence of hemangioblasts and discusses at length why she thinks there is no such thing. Applicant has already indicated on page 2 line 32 to page 3 line 5 that hemangioblasts are controversial in the prior art. In this same passage, Applicant states that he believes hemangioblasts have not been isolated in the art before his invention. This is why the cells he has isolated and demonstrated are novel and useful.

Applicant does not wish to debate whether or not hemangioblasts exist. The claims are amended therefore to delete reference to hemangioblasts. Applicant simply claims what he has actually made, and that is:

> A purified preparation of mammalian cells which
>
> (i) is capable of proliferation in an *in vitro* culture for more than 40 generations, [*see page 29 line 27 to page 30 line 17*]
>
> (ii) does not induce tumor formation in an immunodeficient Rag1-deficient mouse, [*see page 34 line 5 to page 35 line 6*]
>
> (iii) maintains the potential to differentiate to hematopoietic and endothelial cells throughout the duration of said culture, and [*see page 34 line 3 to page 35 line 31*]
>
> (iv) wherein the cells are inhibited from differentiation when cultured on a gelatinized, feeder-free layer. [*see page 29 lines 27 to page 30 line 17; and page 37 lines 23-27*]

The cells' lack of immunohistochemical staining for CD34, PECAM-1 (or CD31), Flk-1, Tie-2, Sca-1, Thy-1 and P-selectin markers (claim 2) is demonstrated at page 32 lines 3-23 and page 38 lines 3-10 and the relevant figures.

The cells that Applicant has actually isolated are shown to have all these features. Applicant submits that the invention as claimed is enabled and was in Applicant's possession as of the filing date.

Biological deposits

The Examiner requires that certain exemplified cells such as HuSH cells, be deposited with an international depositary or otherwise made available to the public. Applicant traverses.

Claims 1-4 do not recite specific cell lines. Applicant has made the specific cell lines designated RoSH2, Ro(BM)SH, HuSH and PoSH, derived from mouse, human and porcine adult bone marrow, respectively. Applicant has deposited RoSH2 with ATCC and claimed the deposited cell line specifically in claim 5. The remaining three cell lines are exemplified cell lines obtained using the methods disclosed in the application. A skilled person following the teaching of the specification would be able to make the cell preparation as claimed without undue experimentation. The cell lines Ro(BM)SH, HuSH and PoSH need not be deposited [see MPEP 2164.06(a)II with reference to *Ex parte Jackson*, 217 USPQ 804, 806 (Bd. App. 1982)].

The address for ATCC is already correctly identified at page 30 lines 20-21.

Applicant submits that the claims comply fully with 35 U.S.C. §112 1st paragraph.

VI. Rejection of claims 1-4 under 35 U.S.C. §112 2nd paragraph

The Examiner rejects claims 1-4 as being indefinite with respect to the term "hemangioblast". The term is deleted from the claims, thereby rendering the rejection moot.

The Examiner rejects claim 2 as being indefinite with respect to the term "PECAM-1 (or CD31)". Applicant traverses. The term is clearly understood in the art. See for example, page 727 column 2 last paragraph of Choi et al. 1998. Development 125:725-732, cited by the Examiner.

Applicant submits that the claims comply fully with 35 U.S.C. §112 2nd paragraph.

VII. Rejection of claims 1-4 under 35 U.S.C. §102(b)

Rafii et al. June 2003 Nature Medicine 9(6):702-712 ('Rafii')

The Examiner rejects claims 1-4 as lacking novelty over Rafii. Applicant traverses.

Rafii is not prior art under 35 U.S.C. §102(b). The reference was published in 2003. The instant application claims the benefit of US 60/453,729 filed July 12, 2002 and US 60/426,789 filed November 18, 2002. The claims are fully supported by the priority applications. Since the claim date precedes the reference date, Rafii is not prior art.

Withdrawal of the rejection in view of Rafii is requested.

Reubinoff et al. 2000 Nature Biotech. 18:399-404 ('Reubinoff')

The Examiner rejects claims 1-4 as lacking novelty over Reubinoff. The Examiner invokes the doctrine of inherent anticipation, stating that Reubinoff's embryonic stem (ES) cells demonstrate "a reasonable probability that they are either identical or sufficiently similar to the claimed cells that whatever differences exist are not patentably significant". Applicant traverses.

The claims require that the preparation of mammalian cells *does not induce tumor formation in an immunodeficient Rag1-deficient mouse*. The cells described by Reubinoff are ES cells; these caused solid tumors in SCID mice (see page 400 column 2 of Reubinoff). Furthermore, the specification actually demonstrates that ES cells, like those of Reubinoff, induce tumors in Rag1-deficient mice (see page 34 lines 14-29, and especially lines 28-29).

Applicant submits that the ES cells described by Reubinoff are different from the cells of the claimed preparation. Withdrawal of the rejection in view of Reubinoff is requested.

Choi et al. 1998. Development 125:725-732 ('Choi')

The Examiner rejects claims 1-4 as lacking novelty over Choi. The Examiner invokes the doctrine of inherent anticipation, stating that Choi's blast-colony forming cells ('blast cells') demonstrate "a reasonable probability that they are either identical or sufficiently similar to the claimed cells that whatever differences exist are not patentably significant". Applicant traverses.

MPEP 2112 IV outlines what is required to establish inherency:

> "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) [....] "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) [...]
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

Claim 2 requires that the cells do not stain for CD34, PECAM-1 (or CD31), Flk-1, Tie-2, Sca-1, Thy-1 and P-selectin markers. By contrast, Choi's blast cells express Flk-1 and CD34 (page 725 2nd column), CD31 (page 727 2nd column middle paragraph), and Tie-2 (page 728 1st column lines 7-10).

The claims require that the cell preparation:

(i) be capable of proliferation in an in vitro culture for more than 40 generations. Choi does not appear to even attempt to culture the blast cells for any significant period of time. The longest period for maintaining the blast cells appears to be 4 days (page 726 2nd column bottom and page 726 1st column lines 7-10).

(ii) not induce tumor formation in an immunodeficient Rag1-deficient mouse, and (iv) that the cells be inhibited from differentiation when cultured on a gelatinized, feeder-free layer. Choi is silent on these features.

(iii) maintain the potential to differentiate to hematopoietic and endothelial cells throughout the duration of said culture. Choi does not test the blast cells' differentiation potential beyond 4 days of growth.

The RoSH cell lines exemplified in the specification were generated from blastocysts after 2-3 weeks on culture plates (see page 28 lines 24-35). By contrast, Choi's blast cells (at page 726 2nd column referring to Kennedy et al. Nature 1997. 386:488-493) were obtained after only 4-6 days after culturing from embryoid bodies (see Kennedy et al. at page 492 under Methods 'Blast colony growth').

In view of the totality of evidence, Applicant submits that the claimed cell preparation is different from the cells described by Choi. The Examiner has not met the burden that the allegedly inherent characteristic(s) necessarily flows from Choi. Withdrawal of the rejection in view of Choi is requested.

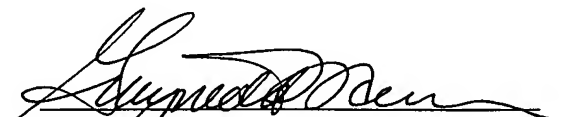
VIII. Concluding Remarks

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. If any questions or issues remain, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

If a fee is required for an extension of time which is not accounted for above, such an extension is requested and the U.S.P.T.O. is authorized to withdraw from our Deposit Account Number 02-4550 any fee required.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 
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Amendments to the Drawings:

The attached drawings (Figures 1-10 on sheets 1/10 – 10/10) are not amended. They are the same drawings originally filed, but are re-printed as to be clearer.

Attachment: Replacement sheets 1/10 to 10/10